RESEARCH REPORT

Continuum of depressive and manic mixed states in patients with bipolar disorder: quantitative measurement and clinical features

ALAN C. SWANN, JOEL L. STEINBERG, MARIJN LIJFFIJT, F. GERARD MOELLER

Department of Psychiatry and Behavioral Sciences, University of Texas Medical School, 1300 Moursund Street, Houston, TX 77030, USA

Bipolar mixed states combine depressive and manic features, presenting diagnostic and treatment challenges and reflecting a severe form of the illness. DSM-IV criteria for a mixed state require combined depressive and manic syndromes, but a range of mixed states has been described clinically. A unified definition of mixed states would be valuable in understanding their diagnosis, mechanism and treatment implications. We investigated the manner in which depressive and manic features combine to produce a continuum of mixed states. In 88 subjects with bipolar disorder (DSM-IV), we evaluated symptoms and clinical characteristics, and compared depression-based, mania-based, and other published definitions of mixed states. We developed an index of the extent to which symptoms were mixed (Mixed State Index, MSI) and characterized its relationship to clinical state. Predominately manic and depressive mixed states using criteria from recent literature, as well as Kraepelinian mixed states, had similar symptoms and MSI scores. Anxiety correlated significantly with depression scores in manic subjects and with mania scores in depressed subjects. Discriminant function analysis associated mixed states with symptoms of hyperactivity and negative cognitions, but not subjective depressive or elevated mood. High MSI scores were associated with severe course of illness. For depressive or manic episodes, characteristics of mixed states emerged with two symptoms of the opposite polarity. This was a cross-sectional study. Mixed states appear to be a continuum. An index of the degree to which depressive and manic symptoms combine appears useful in identifying and characterizing mixed states. We propose a depressive or manic episode with three or more symptoms of the opposite polarity as a parsimonious definition of a mixed state.

Key words: Bipolar disorder, depression, mania, mixed states

(World Psychiatry 2009;8:166-172)

Depressive and manic features can combine during the same episode of bipolar disorder. Patients who are susceptible to mixed states may differ in clinical, illness-course, and treatment response characteristics from those who are not susceptible (1-4). The definition of mixed states and its relationship to depressive and manic syndromes has been elusive. Kraepelin posited six mixed states based on combinations of depressive or manic affect, thought and behavior, resulting in mixed states that could be construed as predominately depressive or manic (5). Subsequent formulations focused on mixed mania, consisting of depressive symptoms during manic episodes (3,6). DSM-IV, for example, requires combined syndromal depression and mania for a mixed state and considers these states to be a form of mania (7).

The mixed mania formulation is problematic. First, clinical reality appears less restrictive than this definition. For example, only two depressive symptoms, not a full mixed state, can alter treatment response during mania (8). Second, there is increasing evidence that depressive mixed states, where manic symptoms occur during a predominately depressive episode, are clinically important and may be at least as prevalent as mixed mania (9). As with predominately manic states, depressive episodes require only two or three manic symptoms to have significant differences in course of illness and clinical characteristics (10,11). In addition to the combination of depressive and manic symptoms, anxiety appears to be a prominent aspect of mixed states (12). Mixed states that are predominately depressive or predominately manic may share clinical characteristics that are relevant to course of illness and response to treatment (13).

We have reported that, during bipolar depressive episodes, increases in severity of the course of illness, impulsivity, and complications like head trauma, substance abuse and attempted suicide emerged with modest levels of manic symptoms (11). If even mild manic symptoms were present, depressive episodes differed substantially from those without manic symptoms in the course of illness and clinical history. Characteristics of patients with mixed manias or mixed depressions suggest that mixed states are symptomatically continuous with depressive and manic states, but have characteristics related to a more severe course of illness. Susceptibility to mixed states may accordingly be a trait characteristic of a subset of patients with severe bipolar disorder (4,14-16). For example, patients with mixed episodes early in the course of illness had a higher prevalence of severe suicide attempts compared to other patients with bipolar disorder (17,18).

Here, we report the manner in which combinations of depressive and manic symptoms produce a continuum of mixed states. The main hypotheses of the study were that: a) clinical correlates of mixed states would be related to severity of manic symptoms in depressed subjects and depressed symptoms in manic subjects; b) the extent to which episodes were mixed could be measured quantitatively and independently of specific depressive or manic symptoms; and c) specific depressive or manic symptoms, related to activation, would be associated with mixed states.

METHODS

Subjects

Subjects were outpatients meeting DSM-IV criteria for bipolar I or II disorder (7). Before they participated in the study, it was thoroughly discussed with them and written informed consent was obtained. The study was reviewed and approved by the Committee for the Protection of Human Subjects, the Institutional Review Board of the University of Texas Houston Health Science Center. Subjects were recruited to cover a range of symptoms and represented euthymic (n=19, mean age 36.0±12.3 years), DSM-IV manic (n=23, age 32.2±9.7 years), DSM-IV depressive (n=28, age 38.2±9.5 years), and mixed states (defined as meeting symptomatic DSM-IV criteria for both depressive and manic states) (n=18, age 36.6±6.0 years). Age did not differ across subject groups ($F(3,84) = 1.4$, $p=0.25$).

Subjects were receiving one or more treatments, including lithium (n=7), anticonvulsants (n=44; predominately valproate and/or lamotrigine), atypical antipsychotics (n=15), or antidepressants (n=31). Seventeen subjects were receiving no psychopharmacological treatments, 30 were receiving one drug class, 26 were receiving two classes, and 5 were receiving three or more classes. Number of drugs was not related to episode type (X^2 (9 df) = 5.3, $p=0.8$). Subjects were studied when specific treatments had not changed, and doses not changed by over 20%, over the previous seven days. Participation in the study had no influence on treatment decisions.

Diagnostic, behavior, and symptom measures

Diagnoses were rendered using the Structured Clinical Interview for DSM-IV (SCID) (19) and confirmed in diagnostic consensus meetings. Symptoms of depression, mania, anxiety, and psychosis were measured using the Change Version of the Schedule for Affective Disorders and Schizophrenia (SADS-C), which was designed to measure these symptom domains concomitantly (20). As discussed in previous work, scores were reduced by one unit so that symptoms were scored as zero if absent, rather than one (8). Personnel were trained, using standard video training materials, in the SCID and SADS-C. DSM-IV mixed states were defined as subjects meeting full symptomatic criteria for manic and major depressive episodes. Symptoms were scored as present if they had a score of at least 2 on the modified SADS-C (mild but definitely present; equivalent to 3 on the original instrument).

For the purposes of identifying subjects in putative depressive or manic mixed states, we excluded SADS-C rating scale items that might, in a circular way, be related to the nominal opposite polarity. Depression item scores used included subjective depression, worry, self-reproach/guilt, negative evaluation of self, hopelessness, suicidal ideation or behavior, anhedonia, fatigue, and psychomotor retardation. Items possibly related to mania, including sleep disturbance, agitation, subjective or objective anger, or irritability, were excluded. Mania item scores included elevated mood, decreased need for sleep, increased energy, manifest anger, goal-directed activity, grandiosity, visible hyperactivity, accelerated speech, racing thoughts, and poor judgment. Anxiety and psychosis factor scores were not used in identifying subjects in mixed states but were compared in mixed vs. non-mixed subjects.

Subjects were defined as euthymic if they did not meet DSM-IV criteria for current depressive or manic episodes and had not had a depressive, hypomanic, or manic episode for at least three months. "Depressed" or "manic" subjects were those who met criteria for a depressive or manic episode, regardless of associated symptoms of the other polarity; subjects whose opposite polarity symptoms were less than relevant threshold criteria are referred to as "non-mixed". A predominately depressed mixed state, DM3, was defined as meeting criteria for a depressive episode and having three or more manic symptoms, corresponding to Benazzi's MX3 (9). A predominately manic state was defined, based on our data on treatment response, as a manic episode with at least three depressive symptoms, which will be referred to here as MD3 (8). Because of the lack of definitive data on duration of specific SADS-C symptoms, one cannot be certain which of these subjects met DSM-IV criteria for a mixed state.

Data analysis

Distributions were checked for normality; if they departed from normal, appropriate non-parametric methods were used. Statistical analyses used standard regression and analysis of variance procedures, or their non-parametric analogs, as described in the text. For correlations of variables whose distributions were not normal, Kendall tau was used, because it was shown to balance power and control of type 1 error more effectively than Pearson or Spearman correlation coefficients (21). Significance of differences between standard correlation coefficients was determined using the Fisher r-z transformation (22).

The extent to which an episode was mixed was estimated using the product of z-transformed depression and mania scores. This is referred to as the Mixed State Index (MSI). The MSI is high if both depression and mania scores are high, but low if either is low (even if the other is high). Z-transformation was used to reduce bias from any difference in numerical values between depression and mania scores (depression scores ranged from 0 to 36, mean 15.3±9.4; mania scores ranged from 0 to 37, mean 10.8±8.6). The absolute value of the minimum z-transformed depression or mania score for all subjects was added to the z-transformed score for each subject so all scores would be non-negative numbers.

Table 1 Symptom severity in predominately depressive or manic mixed states

SADS-C score	Manic (n)		Depressive (n)	
	Non-mixed (n=17)	MD3 (n=24)	Non-mixed (n=27)	DM3 (n=19)
Mania	18.8 ± 7.0	17.4 ± 6.9	4.1 ± 2.5	17.5 ± 7.7*
Depression	8.1 ± 4.7	20.8 ± 7.4**	23.9 ± 5.1	23.7 ± 7.3
Anxiety	7.4 ± 4.0	11.2 ± 3.8***	9.7 ± 3.9	12.0 ± 3.8****
Psychosis	2.2 ± 2.2	3.3 ± 2.5	2.7 ± 1.9	3.6 ± 2.5

SADS-C – Schedule for Affective Disorders and Schizophrenia: Change Version; MD3 – mania with at least three depressive symptoms; DM3 – depression with at least three manic symptoms
Significance of difference by Student's t test: *t(df=44) = 8.4, $p<10^{-6}$; **t(df=39)=6.2, $p<10^{-6}$; ***t(df=39)=3.0, p=0.005; ****t(df=44)=2.0, p=0.058

RESULTS

Mixed mania and mixed depression

DSM-IV defines a mixed state as meeting full criteria for a manic and a major depressive episode, for at least one week. Descriptions of mixed states in the literature, however, include predominant depression with subsyndromal mania (9) and predominant mania with subsyndromal depression (8). Table 1 compares psychiatric symptoms in subjects experiencing a depressive episode with three or more manic symptoms (DM3) (9) and subjects experiencing manic episodes with at least three depressive symptoms (MD3) (8). Anxiety scores correlated positively with mania scores in depressed subjects (r=0.427, n=46, p=0.003) and with depression scores in manic subjects r=0.671, n=41, p=0.001). Mixed states defined as predominately depressive or manic were essentially identical in symptom severity.

Subjects with DM3 or MD3, considered separately, did not differ from corresponding non-mixed depressed or manic subjects with respect to gender (Fisher exact test = 0.52 and 0.23, respectively). However, subjects with either DM3 or MD3 had a greater proportion of women than depressed or manic subjects not in a mixed state (women: 7 non-mixed and 15 mixed; men: 26 non-mixed and 17 mixed; Fisher exact test = 0.028). This confirms earlier reports that patients in broadly defined mixed states are more likely to be women (3,23).

There have been many alternative definitions of mixed states. We investigated two Kraepelinian mixed states (5) that can be considered as varieties of mixed depression (24): depression with flight of ideas (subjects having depressive episodes who also had definite flight of ideas/racing thoughts on SADS-C) and excited depression (depressive episode with hyperactivity on SADS-C). These subjects were essentially identical, in severity of depression, mania, anxiety, and psychosis to the DM3 or MD3 subjects in Table 3. Next, we investigated subjects with at least three depressive symptoms and at least three independent mania symptoms, without the requirement for meeting a full depressive or hypomanic/manic episode. These subjects (n=32) also did not differ in clinical characteristics from those described in Table 2 (data available on request).

Table 2 Mixed State Index (MSI) score and clinical state

	Group (n)	MSI (mean ± SD)
Euthymic (n=19)		0.58 ± 0.53
Depressed	Non-mixed (n=27)	1.53 ± 0.88
	DM3 (n=19)	6.84 ± 4.36
Manic	Non-mixed (n=17)	2.27 ± 1.57
	MD3 (n=24)	6.15 ± 4.10
Mixed (DSM-IV) (n=17)		6.83 ± 4.55

MD3 – mania with at least three depressive symptoms; DM3 – depression with at least three manic symptoms

A Mixed State Index: clinical correlates

The extent to which an episode is mixed can potentially be expressed as the extent to which both depression and mania are present. As defined in Methods, we used the product of z-transformed depression and mania scores as an index of how strongly mixed an episode was (Mixed State Index or MSI). Table 2 compares MSI in subjects experiencing euthymic, depressed, manic, and depression- or mania-based mixed states. MSI was similarly elevated in predominately depressive or manic mixed states. Across all subjects, MSI correlated positively with anxiety (Kendall tau = 0.27, p=0.001) and psychosis (Kendall tau = 0.24, p=0.004).

Figure 1 shows relationships between MSI scores and complications of bipolar disorder. Indices of severe illness, like early onset and suicide attempt, were associated with high MSI scores. Subjects with histories of a substance or alcohol use disorder, however, did not differ from those who had not met criteria for a substance-related disorder.

Depressive and manic symptoms associated with mixed states

In order to determine which specific depressive or manic symptoms were more likely to be associated with being in a mixed state, we conducted a discriminant function analysis using the depression and mania items in the SADS, and a broad classification of mixed states combining MD3 and DM3. After an initial analysis using all SADS depressive and

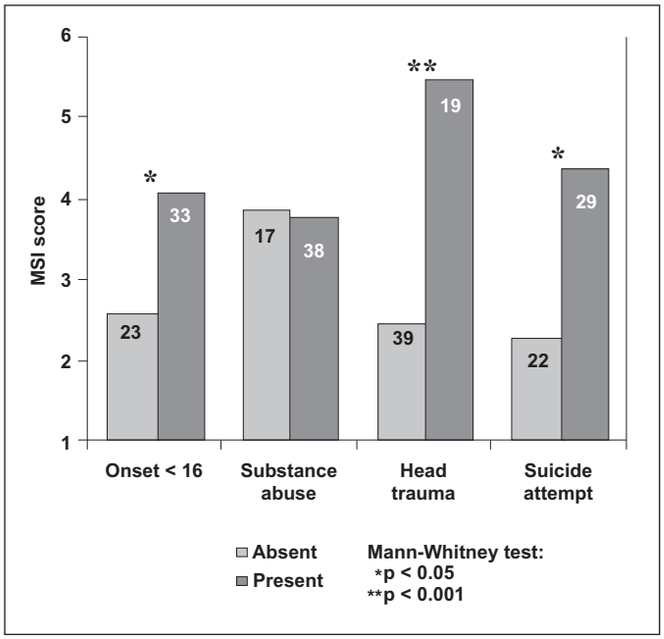

Figure 1 Mixed State Index score and clinical characteristics

manic symptoms, we repeated the analysis using only those symptoms with F>1 to remove from the model. Symptoms in the final group were worry, negative evaluation of self, suicidal ideation or behavior, anhedonia, psychomotor retardation, decreased need for sleep, increased energy, grandiosity, visible hyperactivity, accelerated speech, and racing thoughts. The resultant analysis had Wilks' lambda of 0.38 and overall $F(11,57) = 8.56$ ($p<10^{-4}$). The model classified 90% of cases correctly (86.5% of non-mixed and 93.7% of mixed). Depressive symptoms contributing to the model were worry ($F(1,57)$ to remove = 7.4, p=0.009) and negative evaluation of self (F = 3.74, p=0.05). Manic symptoms were increased energy (F = 5.6, p=0.02), visible hyperactivity (F = 21.9, $p<10^{-4}$), and racing thoughts (F = 5.9, p=0.018).

Thresholds for emergence of "mixed" features

Table 3 summarizes the numbers of depressive or manic symptoms at which differences between mixed and non-mixed episodes become statistically significant. Manic or depressive episodes with two or three symptoms from the opposite polarity differed significantly from those with fewer or no mixed symptoms in terms of symptoms (anxiety and MSI score) and course of illness (history of early onset or suicide attempt).

DISCUSSION

In these subjects with bipolar disorder, a range of predominately depressive or manic mixed state definitions appeared clinically similar, consistent with Kraepelin's suggestion that a greater underlying severity or affective instability drives the emergence of combined symptoms (5). Both depression and mania scores correlated with severity of anxiety in subjects with episodes of the opposite polarity. This underscores previous reports that anxiety is an important component of mixed states (25) and is associated with severe affective symptoms (26). The results suggest that there is a continuum of mixed states.

Dimensional nature of mixed states

The extent to which depressive and manic symptoms combine may be more salient than whether an episode meets DSM-IV criteria for a mixed state, or even whether the combination is predominately depressive or manic. Susceptibility to this combination may be a dimensional characteristic that is associated with greater severity, in terms of duration or treatment resistance of episodes and course of illness. In manic episodes, characteristics like lithium resistance and unstable course of illness emerge at relatively low severity of concomitant depressive symptoms, not requiring full syndromal depression (8). Similar characteristics emerge at relatively low severity of manic symptoms during depressive episodes (11). Even in subjects who have never had free-standing episodes meeting DSM-IV criteria for mania or hypomania, the presence of two or three manic symptoms during a depressive episode confers clinical characteristics resembling bipolar disorder with mixed states rather than unipolar disorder (27). Therefore, we combined depressive and

Table 3 Thresholds for clinical differences between mixed and non-mixed episodes

Number of mixed symptoms	Manic episode				Depressive episode			
	Anxiety	MSI	Suicide attempt	Early onset	Anxiety	MSI	Suicide attempt	Early onset
≥ 1	0.09	0.1	0.35	0.63	**0.003**	**0.001**	0.17	0.49
≥ 2	**0.007**	**0.0007**	0.09	0.18			0.07	0.2
≥ 3			**0.04**	**0.05**			**0.05**	**0.05**

MSI – Mixed State Index

The Table shows probability of t-tests (Anxiety or MSI scores) or Fisher exact test values (history of suicide attempt, onset of illness before age 16) as a function of the number of depressive symptoms in manic episodes or the number of manic symptoms in depressive episodes. Mixed symptoms are the number of depressive symptoms in manic subjects or the number of manic symptoms in depressed subjects

manic symptom scores to form a mixed state index (MSI), using a straightforward combination that would emphasize an interaction between depressive and manic symptoms.

Characteristics of mixed states: specific and nonspecific

Kraepelin described six mixed states, consisting of combinations of depressed or manic affect, thought, and action (5). More recent formulations have focused on mixed mania, corresponding to Kraepelin's depressive or anxious mania (25,28), or mixed depression, corresponding to at least two of Kraepelin's mixed states (24). Multivariate analyses have yielded varying numbers of predominately manic (28,29) or predominately depressive (28,30) mixed states. These states represent permutations of depressive and manic symptoms, whose apparent boundaries depend on the variables and assumptions used in the analyses (31,32).

Mixed mania and mixed depression both have poor response to treatment (33-35), increased risk for suicidal behavior (18,36-38), unstable or severe course of illness (29), and relationship to head trauma or other neurological problems (39,40). Further, mixed states appear not to occur randomly, but tend to recur true to type in susceptible individuals (15,16,41). These properties suggest that susceptibility to mixed states may be related to one or more of: a) pre-existing characteristics (1), possibly genetic (2), that influence course of illness and treatment response; b) consequences of having experienced many episodes (42,43); or c) effects of complications of bipolar disorder like substance abuse or head trauma (39).

Any explanation of susceptibility to mixed states must account for the fact that their symptomatic characteristics vary widely, yet the many symptomatic permutations of mixed states share the clinical and illness-course characteristics described above (13). Clinical characteristics of mixed episodes may result from the interaction between this susceptibility and the unknown factors that determine whether a given episode will be depressive or manic. A parsimonious model could require two characteristics, one related to course of illness, and one to characteristics of individual episodes. The course of bipolar disorder varies widely, but can be described as consisting of two basic types, an "episodic-stable" course and an inherently unstable course that may confer susceptibility to mixed states (1,2,34). In terms of individual episodes, some patients appear to have mostly manic, and others mostly depressive, episodes (44). Mixed states could be predominately depressed or manic, depending on individual characteristics, but would be similar in their relationships to course of illness and to treatment responsiveness.

Subjects who had at least three symptoms of both depression and mania, regardless of whether they met DSM-IV criteria for depressive or manic episodes, resembled subjects in predominately manic or depressed mixed states with respect to severity of psychosis or anxiety. Therefore, one could argue that at least three independent symptoms of depression and of mania define a mixed episode, without the requirement of DSM-IV criteria for depression or mania, and that these episodes are clinically similar or identical to conventionally defined mixed episodes, and may require the same vigorous treatment. This possibility should be investigated further in a larger group of subjects who do not meet full criteria for depressive or manic episodes. Mixed episodes with subsyndromal depressive and manic symptoms may contribute to the poor outcome associated with emergence of subsyndromal symptoms (45).

The data in Figure 1 and Table 3 confirm reports that mixed states are associated with severe course of illness, and suggest that this relationship persists regardless of dominant polarity of the mixed state. The absence of any relationship between mixed features and history of substance-related disorder shown in Figure 1, however, is not consistent with this. However, in interpreting this finding, it is important that the rate of substance use disorder was so high throughout the entire study population (about 70%) that this characteristic may not have been useful in delineating subtypes of illness.

Depressive or manic symptoms and mixed states

Mixed states can be defined equally well using criteria based on symptom rating scale scores or numbers of symptoms present (30). It is of clinical interest, however, to know which depressive or manic symptoms are most likely to be associated with a mixed state. Our data showed that the symptoms distinguishing mixed from non-mixed affective episodes were not primarily mood symptoms but were related to activity (increased energy, visible hyperactivity, racing thoughts) in the case of manic symptoms, and negative cognitions (worry and negative evaluation of self) in the case of depressive symptoms. Which specific symptoms distinguish mixed and non-mixed episodes will depend on the content of the diagnostic or rating measures used. Our data suggest that mixed states are characterized by the combination of negative cognition and hyperactivity, a potentially dangerous combination (36,46).

Specificity of depressive and manic symptom ratings

As noted by Suppes et al (23) in their study of mixed hypomania and reviewed earlier by McElroy et al (3), rating scale items for depressive and manic states may overlap. The SADS-C is designed to minimize this overlap, as it is intended for the simultaneous measurement of depression, mania, anxiety, and psychosis, in contrast to the use of separate individual scales for these entities (20). Items are scored with instructions designed to take clinical context into account. For example, sleep disturbance (which did not figure in the current results) is scored as part of the depression factor unless it is characterized by decreased need for sleep. Agitation is only scored as a depression item if depressive mood or

anhedonia is also present. Nevertheless, we excluded items related to agitation, irritability and anger from depression scores in the identification of predominately manic mixed episodes. The fact that overlap was minimized is confirmed by the lack of correlation between depression and mania scores across all subjects ($r=-0.085$, $n=88$, $p > 0.4$).

Limitations

This was a cross-sectional study, focusing on presence of symptoms at a given time rather than their duration or order of occurrence. The number of subjects limited ability to investigate possible contributing factors reliably. Treatment was not standardized.

CONCLUSIONS

Combined depression and mania, regardless of which predominates, is associated with increased psychosis and anxiety during the current episode, compared with episodes of depression or mania alone. A continuum of mixed states and a metric of susceptibility to these states may describe their characteristics better than a more syndrome-driven categorical model. It will be important to determine the neurobiological mechanisms and clinical course of illness underlying susceptibility to mixed states.

Acknowledgements

This study was supported in part by the Pat R. Rutherford, Jr. Chair in Psychiatry (ACS) and by NIH grants RO1 MH 69944 (ACS), RO1 DA08425 (FGM), and KO2 DA00403 (FGM). We thank Saba Abutaseh, Glen Colton, Stacey Meier, and Mary Pham for their assistance.

References

1. Turvey CL, Coryell WH, Solomon DA et al. Long-term prognosis of bipolar I disorder. Acta Psychiatr Scand 1999;99:110-9.
2. Duffy A, Alda M, Kutcher S et al. A prospective study of the offspring of bipolar parents responsive and nonresponsive to lithium treatment. J Clin Psychiatry 2002;63:1171-8.
3. McElroy SL, Keck PE, Jr., Pope HG, Jr. et al. Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. Am J Psychiatry 1992;149:1633-44.
4. Goldberg JF, McElroy SL. Bipolar mixed episodes: characteristics and comorbidities. J Clin Psychiatry 2007;68:e25.
5. Kraepelin E. Manic-depressive illness and paranoia. Edinburgh: Livingstone, 1921.
6. Kotin J, Goodwin FK. Depression during mania: clinical observations and theoretical implications. Am J Psychiatry 1971;129:55-62.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington: American Psychiatric Association, 1995.
8. Swann AC, Bowden CL, Morris D et al. Depression during mania: treatment response to lithium or divalproex. Arch Gen Psychiatry 1997;54:37-42.
9. Benazzi F. Depressive mixed state: testing different definitions. Psychiatry Clin Neurosci 2001;55:647-52.
10. Benazzi F, Akiskal HS. Delineating bipolar II mixed states in the Ravenna-San Diego collaborative study: the relative prevalence and diagnostic significance of hypomanic features during major depressive episodes. J Affect Disord 2001;67:115-22.
11. Swann AC, Gerard MF, Steinberg JL et al. Manic symptoms and impulsivity during bipolar depressive episodes. Bipolar Disord 2007;9:206-12.
12. Cassidy F, Yatham LN, Berk M et al. Pure and mixed manic subtypes: a review of diagnostic classification and validation. Bipolar Disord 2008;10:131-43.
13. Perugi G, Akiskal HS, Micheli C et al. Clinical characterization of depressive mixed state in bipolar-I patients: Pisa-San Diego collaboration. J Affect Disord 2001;67:105-14.
14. Cassidy F, Ahearn E, Carroll BJ. A prospective study of inter-episode consistency of manic and mixed subtypes of bipolar disorder. J Affect Disord 2001;67:181-5.
15. Dell'Osso L, Placidi GF, Nassi R et al. The manic-depressive mixed state: familial, temperamental and psychopathologic characteristics in 108 female inpatients. Eur Arch Psychiatry Clin Neurosci 1991;240:234-9.
16. Sato T, Bottlender R, Sievers M et al. Evaluating the inter-episode stability of depressive mixed states. J Affect Disord 2004;81:103-13.
17. Khalsa HM, Salvatore P, Hennen J et al. Suicidal events and accidents in 216 first-episode bipolar I disorder patients: predictive factors. J Affect Disord 2008;106:179-84.
18. Valtonen HM, Suominen K, Haukka J et al. Differences in incidence of suicide attempts during phases of bipolar I and II disorders. Bipolar Disord 2008;10:588-96.
19. First MB, Spitzer RL, Gibbon M et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition. New York: Biometrics Research Institute, New York State Psychiatric Institute, 1996.
20. Spitzer RL, Endicott J. Schedule for Affective Disorders and Schizophrenia: Change Version. New York: Biometrics Research, New York State Psychiatric Institute, 1978.
21. Arndt S, Turvey C, Andreasen NC. Correlating and predicting psychiatric symptom ratings: Spearman's r versus Kendall's tau correlation. J Psychiatr Res 1999;33:97-104.
22. Kleinbaum DG, Kupper LL, Muller KE. Applied regression analysis and other multivariate methods. Boston: PWS-Kent, 1988.
23. Suppes T, Mintz J, McElroy SL et al. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Foundation Bipolar Treatment Network: a sex-specific phenomenon. Arch Gen Psychiatry 2005;62:1089-96.
24. Akiskal HS, Benazzi F. Validating Kraepelin's two types of depressive mixed states: "depression with flight of ideas" and "excited depression". World J Biol Psychiatry 2004;5:107-13.
25. Swann AC, Secunda SK, Katz MM. Lithium treatment of mania: clinical characteristics, specificity of symptom change, and outcome. Psychiatry Res 1986;18:127-41.
26. Young LT, Cooke RG, Robb JC et al. Anxious and non-anxious bipolar disorder. J Affect Disord 1993;29:49-52.
27. Akiskal HS, Benazzi F. Family history validation of the bipolar nature of depressive mixed states. J Affect Disord 2003;73:113-22.
28. Cassidy F, Pieper CF, Carroll BJ. Subtypes of mania determined by grade of membership analysis. Neuropsychopharmacology 2001;25:373-83.
29. Swann AC, Janicak PL, Calabrese JR et al. Structure of mania: depressive, irritable, and psychotic clusters with different retrospectively-assessed course patterns of illness in randomized clinical trial participants. J Affect Disord 2001;67:123-32.
30. Benazzi F. Depressive mixed state: dimensional versus categorical definitions. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:129-34.

31. Benazzi F, Koukopoulos A, Akiskal HS. Toward a validation of a new definition of agitated depression as a bipolar mixed state (mixed depression). Eur Psychiatry 2004;19: 85-90.
32. Bertschy G, Gervasoni N, Favre S et al. Phenomenology of mixed states: a principal component analysis study. Bipolar Disord 2007;9: 907-12.
33. Dilsaver SC, Swann AC, Shoaib AM et al. Mixed mania associated with non-response to antimanic agents. Am J Psychiatry 1993;150: 1548-51.
34. Coryell W, Turvey C, Endicott J et al. Bipolar I affective disorder: predictors of outcome after 15 years. J Affect Disord 1998;50:109-16.
35. Maj M, Pirozzi R, Magliano L et al. Agitated "unipolar" major depression: prevalence, phenomenology, and outcome. J Clin Psychiatry 2006;67:712-9.
36. Dilsaver SC, Chen YR, Swann AC et al. Suicidality in patients with pure and depressive mania. Am J Psychiatry 1995;151:1312-5.
37. Akiskal HS, Benazzi F. Does the FDA proposed list of possible correlates of suicidality associated with antidepressants apply to an adult private practice population? J Affect Disord 2006;94:105-10.
38. Balazs J, Benazzi F, Rihmer Z et al. The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention. J Affect Disord 2006;91:133-8.
39. Himmelhoch JM, Mulla D, Neil JF et al. Incidence and severity of mixed affective states in a bipolar population. Arch Gen Psychiatry 1976;33:1062.
40. Swann AC, Moeller FG, Steinberg JL et al. Manic symptoms and impulsivity during bipolar depressive episodes. Bipolar Disord (in press).
41. Cassidy F, Ahearn EP, Carroll BJ. Symptom profile consistency in recurrent manic episodes. Compr Psychiatry 2002;43:179-81.
42. Kessing LV, Hansen MG, Andersen PK et al. The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders - a life-long perspective. Acta Psychiatr Scand 2004;109:339-44.
43. Kessing LV. The prevalence of mixed episodes during the course of illness in bipolar disorder. Acta Psychiatr Scand 2008;117:216-24.
44. Quitkin FM, Rabkin JG, Prien RF. Bipolar disorder: are there manic-prone and depressive-prone forms? J Clin Psychopharmacol 1986;6: 167-72.
45. Keller MB, Lavori PW, Kane JM et al. Subsyndromal symptoms in bipolar disorder. A comparison of standard and low serum levels of lithium. Arch Gen Psychiatry 1992;49:371-6.
46. Swann AC, Dougherty DM, Pazzaglia PJ et al. Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. Am J Psychiatry 2005;162:1680-7.